Neuroscience 299 (2015) 28–34

SEX-SPECIFIC RESTORATION OF MK-801-INDUCED SENSORIMOTOR GATING DEFICIT BY ENVIRONMENTAL ENRICHMENT

M. NOZARI,[a] M. SHABANI,[a] A. M. FARHANGI,[a] S. MAZHARI[a] AND N. ATAPOUR[a,b]*

[a] *Neuroscience Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran*

[b] *Department of Physiology, Monash University, Clayton, Victoria 3800, Australia*

Abstract—Despite ample evidence of N-methyl-D-aspartate (NMDA) receptor dysfunction in schizophrenia, no study has addressed the effects of enriched environment (EE) on sensorimotor gating deficits induced by postnatal NMDA receptor blockade. We evaluated the effect of EE on sensorimotor gating (measured by prepulse inhibition, PPI), or on sensorimotor gating deficit induced by the NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate (MK-801) in both sexes of Wistar rats. Rats were injected with MK-801 (1 mg/kg) on postnatal days (P) 6–10. EE was provided from birth up to the time of experiments on P28–30 or P58–60. PPI data were collected at three prepulse intensities and then averaged to yield global PPI. MK-801 treatment reduced PPI significantly in both sexes. While EE per se had no significant effect on PPI, it restored MK-801-induced PPI deficit only in male rats. An extended period of EE did not influence PPI deficit in female rats. Our results indicate that postnatal exposure to MK-801 may exert long-lasting effects on neuronal circuits underlying sensorimotor gating. Sex-specific modulation of such effects by EE suggests sexually dimorphic mechanisms are involved.

Key words: prepulse inhibition, schizophrenia, NMDA receptor antagonist, rat.

INTRODUCTION

Prepulse inhibition (PPI) of the startle response is characterized by the attenuation of the startle response caused by an intense audiogenic stimulus shortly preceded by a weaker stimulus (Graham, 1975). PPI is a robust operational measure of sensorimotor gating by which excess or trivial stimuli are screened or "gated out" of awareness. Healthy functioning of this mechanism is crucial for normal cognitive processes and several psychiatric disorders, such as schizophrenia are associated with impaired sensorimotor gating, expressed as reduced PPI (Kohl et al., 2013).

Transient neonatal exposure to (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate (MK-801), a non-competitive N-methyl-D-aspartate (NMDA) antagonist, causes deficits in sensorimotor gating of male (Uehara et al., 2009, 2012; Lim et al., 2012) and female rats (Beninger et al., 2002; Harris et al., 2003). Similar changes in PPI have also been reported by acute MK-801 administration in male mice and rats (Long et al., 2006; Khella et al., 2014; Suryavanshi et al., 2014). However, several studies have reported lack of effect of neonatal MK-801 treatment on PPI (Harris et al., 2003; Coleman et al., 2009; Lyall et al., 2009; Su et al., 2011, 2014) and there seems to be a sex factor influencing the PPI outcome with neonatal MK-801 treatment (Harris et al., 2003; Zhao et al., 2013).

Enriched environment (EE) refers to housing conditions in which a combination of complex inanimate and social stimulations is provided to stimulate curiosity and exploration. EE has been shown to facilitate brain development and functions, including sensory, cognitive and motor, under both physiological and pathological conditions (Sale et al., 2014). There are a limited number of studies evaluating the effects of EE on PPI. EE has led to an increase (Chen et al., 2010), decrease (Peña et al., 2009) or no change of PPI (Varty et al., 2000; Schneider et al., 2006; Hoffmann et al., 2009; Guo et al., 2013) in male rats or mice. Pietropaolo et al. (2006) have found that PPI is responsive to EE in adult female mice, although the effect has been bidirectional depending critically on the presence of home-cage running wheels. Two other studies on female rodents have shown no effect (Kulesskaya et al., 2011) or a decrease (Peña et al., 2009) in PPI by EE. To clarify the relevance of sex to the observed differences, in this study we used both male and female rats and directly compared the effects of postnatal MK-801 treatment and EE on PPI. We also looked at the potential preventive effects of EE on PPI deficits in response to postnatal MK-801 treatment, a representative animal model of schizophrenia (Stefani and Moghaddam, 2005; Adell et al., 2012; Balu et al., 2013). PPI restoration by EE has not been addressed previously in this model.

*Correspondence to: N. Atapour, Department of Physiology, Monash University, Clayton, Victoria 3800, Australia.
E-mail address: nafiseh.atapour@monash.edu (N. Atapour).

Abbreviations: CON, control; EE, enriched environment; MK-801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate; MAM, methylazoxymethanol acetate; NMDA, N-methyl-D-aspartate; P, postnatal day; PACAP, pituitary adenylate cyclase-activating polypeptide; PPI, prepulse inhibition.

http://dx.doi.org/10.1016/j.neuroscience.2015.04.050
0306-4522/

EXPERIMENTAL PROCEDURES

Animals

The animals were kept in a room with controlled light (light on at 08:00 a.m. for 12 h) and temperature (21 ± 2 °C) and had free access to food (standard laboratory pellets) and water. All experimental and animal care procedures were performed according to international guidelines on the use of laboratory animals and approved by Kerman University of Medical Sciences Ethics Committee for Animal Research in line with the "NIH Guide for the Care and Use of Laboratory Animals". Maximum efforts were made to minimize animal suffering and to reduce the number of animals used.

A hundred and thirty-four rat pups (68 males and 66 females) from 30 pregnant Wistar rats were used in this study. Each individual pup was assigned a number after birth and this number was used for marking throughout the experiments. On postnatal (P) day 4, litters were culled to a maximum of six same-sex pups (male or female) per dam. After the removal of the dam on P21, the same number of pups remained in each cage in either control (CON) or EE conditions. For each sex, rats were divided into four groups randomly: (1) CON rats were housed in standard laboratory cages (40 × 20 × 15 cm). (2) EE rats were housed in large cages (60 × 30 × 20 cm) with a wire mesh lid containing running wheels and differently shaped objects (e.g., tunnels, shelters, stairs) from birth up to the time of experiments. Toys were changed every week. (3) MK-801-treated rats, housed in standard laboratory cages, received a single injection of MK-801 per day (1 mg/kg, i.p., purchased from Tocris and dissolved in saline), repeated for 5 days from P6–10 (Turner et al., 2010). (4) EE + MK-801 rats were raised in EE cages and received MK-801 injections as described above. In parallel with MK-801 injections, rats in CON and EE groups received saline injections once per day on P6–10. Half of the pups in the same litter group either in standard or EE cages received MK-801 treatment in a random order and the other half received saline. We did not observe any obvious changes in the maternal behavior as a function of housing manipulation. All animals were housed in the respective mentioned environments up to the time of behavioral testing on P28–30 (early adolescence, both sexes) or P58–60 (early adulthood, females only). All animals tested were at a range of 45–50 g on P28–30 and 100–110 g on P58–60. PPI test was performed between 08:00 a.m. and 13:00 p.m. and all female rats were in the same point of estrous cycle at the time of testing.

PPI

Equipment. Auditory startle reflex amplitude and PPI were measured using Med Associates Startle Reflex System (St. Albans, VT, USA). The equipment included: a response platform (piezoelectric accelerometer) that was placed in sound attenuating chamber, a speaker that was placed within the chamber midway on the long axis of the platform and a plexiglas cylinder which was mounted on the platform. Animal movement is detected and transduced by a piezoelectric accelerometer under the cylinder. This movement produces a sinusoidal motion pattern, so startle amplitudes were taken from the maximum peak to the minimum peak of the sinusoidal response. Background noise was set to 68 dB.

Behavioral procedure. The test session utilized consisted of the following components: a 5-min acclimation period to a 68-dB background noise which began when the animals were placed in the chambers and continued throughout the entire session; 14 PULSE-ALONE trials in which a 40-ms, 120-dB broadband noise burst was presented; 30 PREPULSE + PULSE trials in which the onset of a 20-ms broadband noise prepulse preceded the onset of the 120-dB pulse by 100 ms (10 for each of prepulse intensities of 71, 74, and 80 dB; 3, 6 and 12 dB above the background noise respectively); and eight NO-STIMULUS trials consisted of only the background noise. Prepulse intensities used in our protocol did not induce startle reaction. All trials were presented in a pseudo-random order with an average of a 22-s (15–30 s range) inter-trial interval. Four 120-dB pulse trials were presented at the beginning and the end of the test session (for a total of 60 trials), but were not used in the calculation of PPI values (Valsamis and Schmid, 2011).

The level of PPI was calculated as a percentage score for each prepulse. The formula for this calculation is: %PPI = 100 − {[(startle response for PREPULSE + PULSE trial) / (startle response for PULSE-ALONE trial)] × 100} (Powell et al., 2003). Global PPI was considered as an overall measure of the observed treatment for which percent PPI data were averaged across the three prepulses for each rat (Ces et al., 2012).

Statistical analysis

We tested homogeneity of variances using Levene's test and since the resulting p-value was bigger than $p > 0.05$ and exhibited homoscedasticity, we performed a parametric test of ANOVA. PPI results of P28–30 rats were analyzed by a three-way repeated measures ANOVA considering group (MK-801, EE treatment included) and sex as between-subject factors and prepulse intensity as a within-subject (repeated measures) factor. A two-way ANOVA was used to compare global PPI data as well as startle response amplitude of male and female rats on P28–30. A two-way repeated measures ANOVA was used to compare global PPI as well as startle response amplitude of female rats at two ages of P28–30 and P58–60. Post-hoc comparisons were made using Fisher's LSD test. All computations were made using the statistical package of SPSS (IBM, Version 20) and the difference with p-values less than 0.05 was considered statistically significant. The results are expressed as mean ± SEM.

RESULTS

Sex differences in response to MK-801 and EE on P28–30

The three-way ANOVA showed only a significant main effect of prepulse intensity [$F(2, 252) = 35.3$, $p < 0.001$] and there was no significant interaction between prepulse intensity × group, prepulse intensity × sex and prepulse intensity × group × sex. Tests between subjects showed the main effect of group [$F(3, 126) = 10.534$, $p < 0.001$] and sex [$F(1, 126) = 6.756$, $p < 0.01$], but no interaction of group × sex was observed. Since prepulse intensity did not interact with any of the other variables (MK-801 treatment, EE and sex) significantly, PPI was collapsed across intensities as "global PPI" and were analyzed using a two-way ANOVA. These analyses revealed a significant main effect of sex [$F(1, 126) = 6.75$, $p = 0.01$]) and treatment [$F(3, 126) = 10.53$, $p < 0.0001$] without a significant interaction between treatment × sex. Post hoc analysis revealed a significant decrease in PPI of male ($p < 0.05$, Fig. 1a) and female ($p < 0.001$, Fig. 1b) MK-801-treated rats compared to the CON group.

EE per se did not affect PPI significantly but prevented MK-801-induced PPI deficit in male rats and PPI in EE + MK-801 rats was significantly different from the MK-801 group ($p < 0.05$, Fig. 1a), but not the CON group ($p > 0.05$). However, such a restoration of PPI by EE was not observed in female rats and PPI in EE + MK-801 rats was not significantly different from that in the MK-801 group ($p > 0.05$, Fig. 1b).

An analysis of baseline startle response amplitudes with a two-way ANOVA revealed a significant effect of treatment [$F(3, 126) = 20.56$, $p < 0.0001$] with no effect of sex, or interaction between treatment × sex. Post hoc analysis showed that MK-801 treatment led to a significantly higher startle response in both sexes when compared to CON ($p < 0.05$ for males and $p < 0.001$ for females, Fig. 1c, d). EE did not prevent MK-801-induced startle response enhancement. In male rats, startle response of the EE + MK-801 group was significantly higher than that of other groups ($p < 0.01$ compared to the MK-801 group and $p < 0.0001$ compared to CON and EE groups, Fig. 1c). In females, startle response of the EE + MK-801 group was significantly higher than that of CON ($p < 0.001$) and EE groups ($p < 0.001$, Fig. 1d).

Prolonged EE does not protect female rats against MK-801-induced PPI deficit

Since we did not observe a significant positive effect of EE on PPI deficit in female rats on P28–30, we continued EE

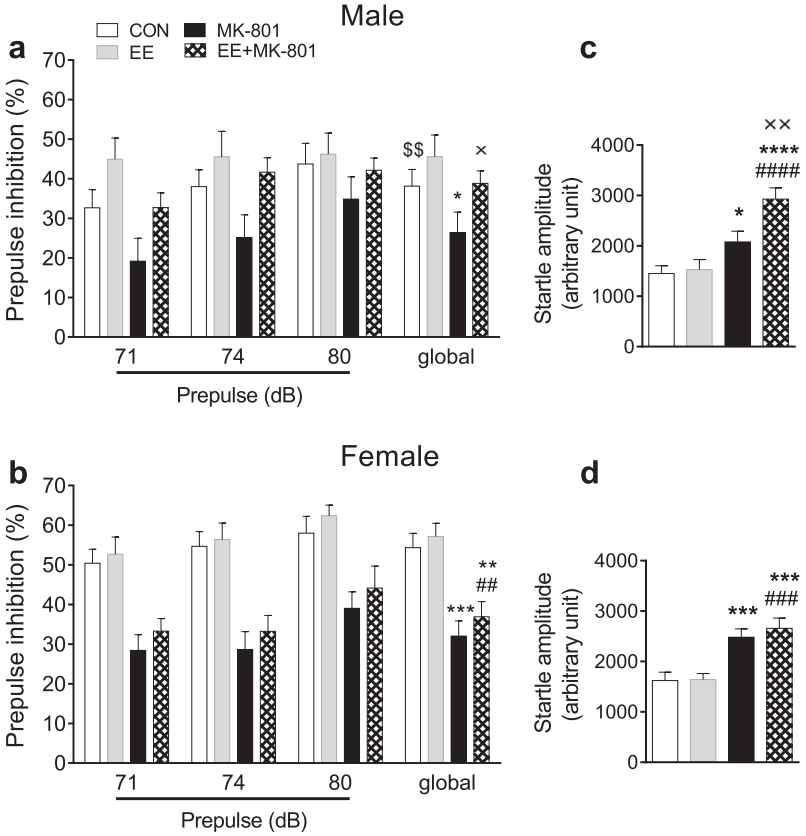

Fig. 1. Effects of postnatal MK-801 treatment and enriched environment (EE) on prepulse inhibition (PPI) of male and female rats on P28–30. Mean ± SEM of PPI in control (CON), EE, MK-801-treated, and EE + MK-801 groups of male (a) and female (b) rats are shown for three prepulses and global PPI. Mean startle response in male (c) and female (d) rats. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ compared to CON, $^{\times}p < 0.05$, $^{\times\times}p < 0.01$ compared to MK-801, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, $^{\#\#\#\#}p < 0.0001$ compared to EE, $^{\$\$}p < 0.01$ male compared to female. Males, $n = 20$ for CON, $n = 17$ for EE, $n = 16$ for MK-801 and $n = 15$ for EE + MK-801 group; females, $n = 20$ for CON, $n = 15$ for EE, $n = 18$ for MK-801 and $n = 13$ for EE + MK-801 group.

application in these rats for another 30 days and tested them again on P58–60. A two-way repeated measures ANOVA showed a significant main effect of treatment [$F(3, 48) = 17.29$, $p < 0.0001$] but no significant effect of age or interaction between treatment × age was observed. Post hoc analysis demonstrated that MK-801 treatment resulted in a significant reduction of PPI on P58–60 ($p < 0.0001$, Fig. 2d). However, EE did not influence PPI of female rats on P58–60, either alone or induced by MK-801 ($p > 0.05$, Fig. 2d). These results suggest that postnatal MK-801-induced PPI deficit in females is present at adulthood and longer periods of EE cannot restore PPI.

An analysis of startle response of female rats in two age groups (P28–30 vs. P58–60) was made using a two-way repeated measures ANOVA. While there was a significant effect of age [$F(1, 48) = 25.75$, $p < 0.0001$] and treatment [$F(3, 48) = 7.62$, $p = 0.0003$], no significant effect of interaction between them was observed. Post hoc analysis showed that on P58–60, MK-801 treatment did not result in a significantly higher startle response compared to that of CON ($p > 0.05$), but mean startle response in the EE + MK-801 group was significantly higher than that of CON ($p < 0.05$) and EE groups ($p < 0.001$, Fig. 2e). On P58–60, startle response was significantly higher than that of P28–30 in all groups except the MK-801-treated group ($p < 0.01$ for CON group and $p < 0.05$ for EE and EE + MK-801 groups, not shown on the graph). This significant increase in startle response can be explained by weight gained by these animals during this timing.

DISCUSSION

The present study demonstrates that transient, postnatal exposure to MK-801 induces disruption of sensorimotor gating measured by PPI in both sexes. EE restores PPI deficits induced by MK-801 treatment uniquely in male rats.

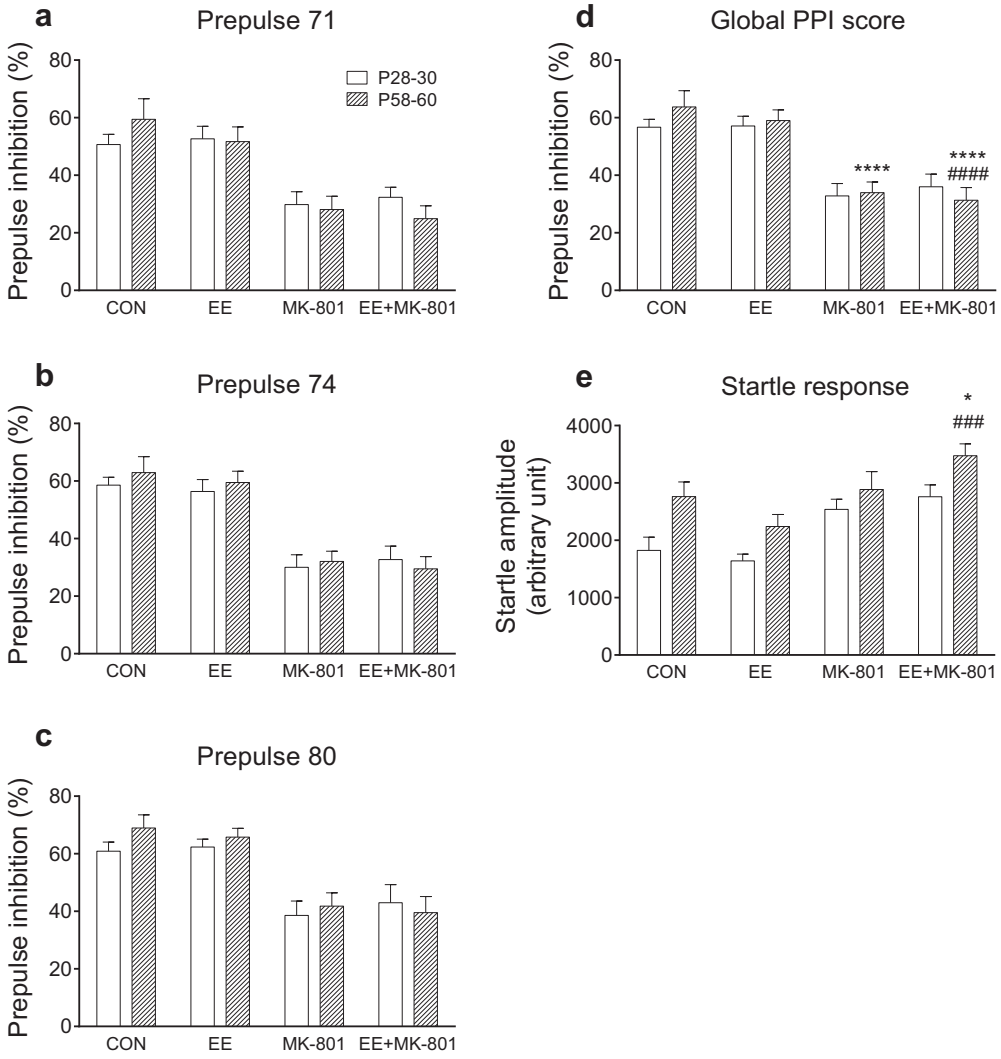

Fig. 2. An extended period of enriched environment (EE) did not influence reduced prepulse inhibition (PPI) in MK-801-treated female rats. Mean ± SEM of PPI in control (CON), EE, MK-801-treated, and EE + MK-801 groups on P28–30 and P58–60 is shown for three prepulses (a–c) and global PPI (d). Mean startle response (e). $^{*}p < 0.05$, $^{****}p < 0.0001$ compared to CON; $^{\#\#\#}p < 0.001$, $^{\#\#\#\#}p < 0.0001$ compared to EE. $n = 11$ for CON and EE + MK-801 groups, $n = 15$ for EE and MK-801 groups. Comparisons of different groups on P58–60 are shown only.

PPI of the startle response is impaired in certain psychiatric disorders, particularly in schizophrenia. Symptoms of schizophrenia typically begin to emerge at adolescence in most of the patients; therefore we tested animals on P28–30 to assess the sensorimotor gating at early adolescence. Observed baseline PPI values in both sexes in our study are consistent with observation of many other groups (Beninger et al., 2002; Harris et al., 2003; Uehara et al., 2009; Su et al., 2011, 2014).

Most of the previous studies using postnatal MK-801 treatment have shown PPI deficit in either male or female rats and particularly in the post-puberty stage (Geyer et al., 2001; Beninger et al., 2002; Harris et al., 2003; Uehara et al., 2009, 2012; Lim et al., 2012). Our study showed that PPI deficit could be reliably induced in both sexes as early as P28–30. Low dosages of MK-801 in some studies could be the reason behind ineffectiveness of this treatment on PPI (Harris et al., 2003; Coleman et al., 2009; Lyall et al., 2009; Su et al., 2011, 2014). In view of the NMDA hypothesis of schizophrenia (Stefani and Moghaddam, 2005; Balu et al., 2013), our findings indicate that this protocol of postnatal MK-801 treatment is useful for the study of the pathophysiology of schizophrenia. It reduces PPI, as an endophenotype of the disease and also induces cognitive and locomotor deficits representative of other symptoms of schizophrenia (Nozari et al., 2014, 2015).

Despite the vast literature on positive effects of EE on the brain and behavior, few studies have assessed the effects of EE on sensorimotor gating in rodents. These studies whether in males or females, have reported an increase, decrease or no effect of EE on PPI (Varty et al., 2000; Pietropaolo et al., 2006; Schneider et al., 2006; Hoffmann et al., 2009; Peña et al., 2009; Chen et al., 2010; Emack and Matthews, 2011; Kulesskaya et al., 2011; Guo et al., 2013). We did not observe a significant effect of EE on PPI in either sex. Thus it seems that the capacity of positive environmental factors to modulate rat brain circuits involved in sensorimotor gating is limited. Observed differences with other works may reflect on different species, experimental conditions and also multiple EE paradigms (Turner and Burne, 2013).

Surprisingly no attempt has been made to assess the effect of EE on PPI impairment induced by NMDA receptor antagonists although the accumulating evidence suggests that many of the behavioral abnormalities associated with schizophrenia may be due to a dysfunctional NMDA receptor system (for a review, see Snyder and Gao, 2013). EE has been shown to rescue PPI deficit in phospholipase C-β1 KO mice (McOmish et al., 2008) and methylazoxymethanol acetate (MAM)-treated male mice (Guo et al., 2013) but not in pituitary adenylate cyclase-activating polypeptide (PACAP)-deficient male mice (Ishihama et al., 2010). Here we show a rescue effect of PPI in the postnatal MK-801 model of schizophrenia, exclusive to male rats. Mechanisms through which EE can rescue PPI are not known, however the work of Guo et al. (2013) suggests that the effects of EE may be applied through postnatal neurogenesis and modification of inhibitory circuits during critical periods of development. Infusion of muscimol, a $GABA_A$ receptor agonist, into the DG region reversed PPI abnormality in MAM-treated mice similar to the rescue effect observed by EE in the same study (Guo et al., 2013). Perinatal NMDA receptor blockades could induce deficits of excitatory and inhibitory neurotransmissions during brain development and might result in the disinhibition of pyramidal neurons (Du Bois et al., 2009). Multiple limbic forebrain regions (the prefrontal cortex, hippocampus and amygdala) mediate the ability of non-competitive NMDA antagonists to disrupt PPI (Bakshi and Geyer, 1998) and therefore EE might influence excitatory–inhibitory circuitry in any of these structures to rescue the deficit.

Sex-specific behavioral effects of EE have been previously reported in animal models of diseases such as experimental brain trauma (Wagner et al., 2002) or in a transgenic mouse model of amyotrophic lateral sclerosis (Stam et al., 2008). In our study, sex differences in restoration of PPI deficit by EE may be driven by hormonally mediated mechanisms, differences in the production of growth factors or their interaction (Berchtold et al., 2001; du Bois et al., 2009; Gogos et al., 2012; Guo et al., 2013). Estrogen seems to be a key player in controlling PPI levels in females (Koch, 1998). It might enhance neuronal firing and affect the forebrain modulation of PPI (Parducz et al., 2002). Another contributing factor may be a marked sex difference in MK-801 metabolism reported by Andiné et al. (1999). They have reported, 3–5 h after acute injection of MK-801, female rats display higher serum and brain concentrations of MK-801 compared to male rats. Although we tested animals almost 20 days after last MK-801 injection, it is likely that a higher concentration of MK-801 after injection contributed to more significant damages irreversible to the effects of EE. However, we recently showed that EE can rescue locomotor/anxiety-related deficits (observed in the open field test) but not cognitive deficits in female rats by the same method of MK-801 application (Nozari et al., 2015). PPI might reflect a more general filtering performance leading to gating of intrusive inputs to improve cognitive function; therefore it is not surprising if EE did not restore PPI deficits in females. A higher concentration of MK-801 in the serum of females is expected to contribute to greater female susceptibility reported for PPI reduction (Zhao et al., 2013), locomotor behaviors (Hönack and Löscher, 1993; Andiné et al., 1999; Feinstein and Kritzer, 2013) and neuronal cytotoxicity (Auer, 1996). However, we did not observe significant sex differences for PPI reduction by MK-801 in this study. Taken together, the lack of effect of EE in rescuing deficits of PPI in females may represent more complex alterations in related neuronal circuitry.

While startle response amplitudes were not affected by sex or EE, we observed significant enhancement of startle response by MK-801 in both males and females (only on P28–30) possibly as a result of heightened anxiety in these animals (Amani et al., 2013; Nozari et al., 2014). This is consistent with previous studies that have shown a higher level of anxiety led to greater strength of the acoustic startle response (Davis et al., 1997; Plappert and Pilz, 2002). This enhancement of

startle response was not compensated by EE application in either male or female EE + MK-801 rats. However, a significant PPI reduction by MK-801 in both sexes despite an enhanced startle amplitude suggests that the initial startle response was not predictive of the PPI values. This is further confirmed by the fact that, despite similar alterations in the startle amplitude of male and female EE + MK-801 rats, EE application restored deficient PPI to CON levels only in male rats.

CONCLUSION

Taken together, an early-life blockade of the NMDA receptors by MK-801 induces behavioral changes that mimic several features of schizophrenia including disrupted PPI which is subject to modulation by EE in a sex-specific way. These data strengthen the importance of taking into account sex differences in animal models of schizophrenia. Future studies should address the mechanisms mediating differential effects of EE on male and female brain circuits.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

Acknowledgment—This research article is part of the first author's Ph.D. thesis. Funding for this study was provided by Neuroscience Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran.

REFERENCES

Adell A, Jiménez-Sánchez L, López-Gil X, Romón T (2012) Is the acute NMDA receptor hypofunction a valid model of schizophrenia? Schizophr Bull 38:9–14. http://dx.doi.org/10.1093/schbul/sbr133.

Amani M, Samadi H, Doosti MH, Azarfarin M, Bakhtiari A, Majidi-Zolbanin N, Mirza-Rahimi M, Salari AA (2013) Neonatal NMDA receptor blockade alters anxiety- and depression-related behaviors in a sex-dependent manner in mice. Neuropharmacology 73:87–97. http://dx.doi.org/10.1016/j.neuropharm.2013.04.056.

Andiné P, Widermark N, Axelsson R, Nyberg G, Olofsson U, Mårtensson E, Sandberg M (1999) Characterization of MK-801-induced behavior as a putative rat model of psychosis. J Pharmacol Exp Ther 290(3):1393–1408.

Auer RN (1996) Effect of age and sex on N-methyl-D-aspartate antagonist-induced neuronal necrosis in rats. Stroke 27(4):743–746.

Bakshi VP, Geyer MA (1998) Multiple limbic regions mediate the disruption of prepulse inhibition produced in rats by the noncompetitive NMDA antagonist dizocilpine. J Neurosci 18(20):8394–8401.

Balu DT, Li Y, Puhl MD, Benneyworth MA, Basu AC, Takagi S, Bolshakov VY, Coyle JT (2013) Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction. Proc Natl Acad Sci U S A 110(26):E2400–E2409. http://dx.doi.org/10.1073/pnas.1304308110.

Beninger RJ, Jhamandas A, Aujla H, Xue L, Dagnone RV, Boegman RJ, Jhamandas K (2002) Neonatal exposure to the glutamate receptor antagonist MK-801: effects on locomotor activity and pre-pulse inhibition before and after sexual maturity in rats. Neurotox Res 4(5–6):477–488.

Berchtold NC, Kesslak JP, Pike CJ, Adlard PA, Cotman CW (2001) Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. Eur J Neurosci 14(12):1992–2002.

Ces A, Reiss D, Walter O, Wichmann J, Prinssen EP, Kieffer BL, Ouagazzal AM (2012) Activation of nociceptin/orphanin FQ peptide receptors disrupts visual but not auditory sensorimotor gating in BALB/cByJ mice: comparison to dopamine receptor agonists. Neuropsychopharmacology 37(2):378–389. http://dx.doi.org/10.1038/npp.2011.175.

Chen Y, Mao Y, Zhou D, Hu X, Wang J, Ma Y (2010) Environmental enrichment and chronic restraint stress in ICR mice: effects on prepulse inhibition of startle and Y-maze spatial recognition memory. Behav Brain Res 212(1):49–55. http://dx.doi.org/10.1016/j.bbr.2010.03.033.

Coleman Jr LG, Jarskog LF, Moy SS, Crews FT (2009) Deficits in adult prefrontal cortex neurons and behavior following early post-natal NMDA antagonist treatment. Pharmacol Biochem Behav 93(3):322–330. http://dx.doi.org/10.1016/j.pbb.2009.04.017.

Davis M, Walker DL, Lee Y (1997) Roles of the amygdala and bed nucleus of the stria terminalis in fear and anxiety measured with the acoustic startle reflex. Possible relevance to PTSD. Ann N Y Acad Sci 821:305–331. Review.

du Bois TM, Deng C, Han M, Newell KA, Huang XF (2009) Excitatory and inhibitory neurotransmission is chronically altered following perinatal NMDA receptor blockade. Eur Neuropsychopharmacol 19(4):256–265. http://dx.doi.org/10.1016/j.euroneuro.2008.12.002.

Emack J, Matthews SG (2011) Effects of chronic maternal stress on hypothalamo-pituitary-adrenal (HPA) function and behavior: no reversal by environmental enrichment. Horm Behav 60(5):589–598. http://dx.doi.org/10.1016/j.yhbeh.2011.08.008.

Feinstein I, Kritzer MF (2013) Acute N-methyl-D-aspartate receptor hypofunction induced by MK801 evokes sex-specific changes in behaviors observed in open-field testing in adult male and proestrus female rats. Neuroscience 228:200–214. http://dx.doi.org/10.1016/j.neuroscience.2012.10.026.

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology (Berl) 156(2–3):117–154. Review.

Graham FK (1975) The more or less startling effects of weak prestimulation. Psychophysiology 12(3):238–248.

Gogos A, Kwek P, van den Buuse M (2012) The role of estrogen and testosterone in female rats in behavioral models of relevance to schizophrenia. Psychopharmacology (Berl) 219(1):213–224. http://dx.doi.org/10.1007/s00213-011-2389-y.

Guo N, Yoshizaki K, Kimura R, Suto F, Yanagawa Y, Osumi N (2013) A sensitive period for GABAergic interneurons in the dentate gyrus in modulating sensorimotor gating. J Neurosci 33(15):6691–6704. http://dx.doi.org/10.1523/JNEUROSCI.0032-12.2013.

Harris LW, Sharp T, Gartlon J, Jones DN, Harrison PJ (2003) Long-term behavioural, molecular and morphological effects of neonatal NMDA receptor antagonism. Eur J Neurosci 18(6):1706–1710.

Hoffmann LC, Schütte SR, Koch M, Schwabe K (2009) Effect of "enriched environment" during development on adult rat behavior and response to the dopamine receptor agonist apomorphine. Neuroscience 158(4):1589–1598. http://dx.doi.org/10.1016/j.neuroscience.

Hönack D, Löscher W (1993) Sex differences in NMDA receptor mediated responses in rats. Brain Res 620(1):167–170.

Ishihama T, Ago Y, Shintani N, Hashimoto H, Baba A, Takuma K, Matsuda T (2010) Environmental factors during early developmental period influence psychobehavioral abnormalities in adult PACAP-deficient mice. Behav Brain Res 209(2):274–280. http://dx.doi.org/10.1016/j.bbr.2010.02.009.

Khella R, Short JL, Malone DT (2014) CB (2) receptor agonism reverses MK-801-induced disruptions of prepulse inhibition in mice. Psychopharmacology (Berl). PubMed PMID: 24705902.

Koch M (1998) Sensorimotor gating changes across the estrous cycle in female rats. Physiol Behav 64(5):625–628.

Kohl S, Heekeren K, Klosterkötter J, Kuhn J (2013) Prepulse inhibition in psychiatric disorders – apart from schizophrenia. J Psychiatr Res 47(4):445–452. http://dx.doi.org/10.1016/j.jpsychires.

Kulesskaya N, Rauvala H, Voikar V (2011) Evaluation of social and physical enrichment in modulation of behavioural phenotype in C57BL/6J female mice. PLoS One 6(9):e24755. http://dx.doi.org/10.1371/journal.pone.0024755.

Lim AL, Taylor DA, Malone DT (2012) A two-hit model: behavioural investigation of the effect of combined neonatal MK-801 administration and isolation rearing in the rat. J Psychopharmacol 26(9):1252–1264. http://dx.doi.org/10.1177/0269881111430751.

Long LE, Malone DT, Taylor DA (2006) Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice. Neuropsychopharmacology 31(4):795–803.

Lyall A, Swanson J, Liu C, Blumenthal TD, Turner CP (2009) Neonatal exposure to MK-801 promotes prepulse-induced delay in startle response time in adult rats. Exp Brain Res 197(3):215–222. http://dx.doi.org/10.1007/s00221-009-1906-2.

McOmish CE, Burrows E, Howard M, Scarr E, Kim D, Shin HS, Dean B, van den Buuse M, Hannan AJ (2008) Phospholipase C-beta1 knockout mice exhibit endophenotypes modeling schizophrenia which are rescued by environmental enrichment and clozapine administration. Mol Psychiatry 13(7):661–672.

Nozari M, Shabani M, Hadadi M, Atapour N (2014) Enriched environment prevents cognitive and motor deficits associated with postnatal MK-801 treatment. Psychopharmacology (Berl) 231(22):4361–4370. http://dx.doi.org/10.1007/s00213-014-3580-8.

Nozari M, Mansouri FA, Shabani M, Nozari H, Atapour N (2015) Postnatal MK-801 treatment of female rats impairs acquisition of working memory, but not reference memory in an 8-arm radial maze; no beneficial effects of enriched environment. Psychopharmacology (Berl). http://dx.doi.org/10.1007/s00213015 38905.

Parducz A, Hoyk Z, Kis Z, Garcia-Segura LM (2002) Hormonal enhancement of neuronal firing is linked to structural remodelling of excitatory and inhibitory synapses. Eur J Neurosci 16(4):665–670.

Peña Y, Prunell M, Rotllant D, Armario A, Escorihuela RM (2009) Enduring effects of environmental enrichment from weaning to adulthood on pituitary-adrenal function, pre-pulse inhibition and learning in male and female rats. Psychoneuroendocrinology 34(9):1390–1404. http://dx.doi.org/10.1016/j.psyneuen.2009.04.019.

Pietropaolo S, Feldon J, Alleva E, Cirulli F, Yee BK (2006) The role of voluntary exercise in enriched rearing: a behavioral analysis. Behav Neurosci 120(4):787–803.

Plappert CF, Pilz PK (2002) Difference in anxiety and sensitization of the acoustic startle response between the two inbred mouse strains BALB/cAN and DBA/2N. Genes Brain Behav 1(3):178–186.

Powell SB, Geyer MA, Preece MA, Pitcher LK, Reynolds GP, Swerdlow NR (2003) Dopamine depletion of the nucleus accumbens reverses isolation-induced deficits in prepulse inhibition in rats. Neuroscience 119(1):233–240.

Sale A, Berardi N, Maffei L (2014) Environment and brain plasticity: towards an endogenous pharmacotherapy. Physiol Rev 94(1):189–234. http://dx.doi.org/10.1152/physrev.00036.2012. Review.

Schneider T, Turczak J, Przewłocki R (2006) Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: issues for a therapeutic approach in autism. Neuropsychopharmacology 31(1):36–46.

Snyder MA, Gao WJ (2013) NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia. Front Cell Neurosci 7:31. http://dx.doi.org/10.3389/fncel.2013.00031.

Stam NC, Nithianantharajah J, Howard ML, Atkin JD, Cheema SS, Hannan AJ (2008) Sex-specific behavioural effects of environmental enrichment on a transgenic mouse model of amyotrophic lateral sclerosis. Eur J Neurosci 28(4):717–723. http://dx.doi.org/10.1111/j.1460-9568.2008.06374.x.

Stefani MR, Moghaddam B (2005) Transient N-methyl-D-aspartate receptor blockade in early development causes lasting cognitive deficits relevant to schizophrenia. Biol Psychiatry 57(4):433–436.

Su YA, Huang RH, Wang XD, Li JT, Si TM (2014) Impaired working memory by repeated neonatal MK-801 treatment is ameliorated by galantamine in adult rats. Eur J Pharmacol 725:32–39. http://dx.doi.org/10.1016/j.ejphar.2014.01.007.

Su YA, Wang XD, Li JT, Guo CM, Feng Y, Yang Y, Huang RH, Si TM (2011) Age-specific effects of early MK-801 treatment on working memory in female rats. Neuroreport 22(8):402–406. http://dx.doi.org/10.1097/WNR.0b013e328346e154.

Suryavanshi PS, Ugale RR, Yilmazer-Hanke D, Stairs DJ, Dravid SM (2014) GluN2C/GluN2D subunit-selective NMDA receptor potentiator CIQ reverses MK-801-induced impairment in prepulse inhibition and working memory in Y-maze test in mice. Br J Pharmacol 171(3):799–809. http://dx.doi.org/10.1111/bph.12518.

Turner KM, Burne TH (2013) Interaction of genotype and environment: effect of strain and housing conditions on cognitive behavior in rodent models of schizophrenia. Front Behav Neurosci 7:97. http://dx.doi.org/10.3389/fnbeh.2013.00097.

Turner CP, DeBenedetto D, Ware E, Stowe R, Lee A, Swanson J, Walburg C, Lambert A, Lyle M, Desai P, Liu C (2010) Postnatal exposure to MK801 induces selective changes in GAD67 or parvalbumin. Exp Brain Res 201(3):479–488. http://dx.doi.org/10.1007/s00221-009-2059.

Uehara T, Sumiyoshi T, Hattori H, Itoh H, Matsuoka T, Iwakami N, Suzuki M, Kurachi M (2012) T-817MA, a novel neurotrophic agent, ameliorates loss of GABAergic parvalbumin-positive neurons and sensorimotor gating deficits in rats transiently exposed to MK-801 in the neonatal period. J Psychiatr Res 46(5):622–629. http://dx.doi.org/10.1016/j.jpsychires.2012.01.022.

Uehara T, Sumiyoshi T, Seo T, Itoh H, Matsuoka T, Suzuki M, Kurachi M (2009) Long-term effects of neonatal MK-801 treatment on prepulse inhibition in young adult rats. Psychopharmacology (Berl) 206(4):623–630. http://dx.doi.org/10.1007/s00213-009-1527-2.

Valsamis B, Schmid S (2011) Habituation and prepulse inhibition of acoustic startle in rodents. J Vis Exp(55):e3446. http://dx.doi.org/10.3791/3446.

Varty GB, Paulus MP, Braff DL, Geyer MA (2000) Environmental enrichment and isolation rearing in the rat: effects on locomotor behavior and startle response plasticity. Biol Psychiatry 47(10):864–873.

Wagner AK, Kline AE, Sokoloski J, Zafonte RD, Capulong E, Dixon CE (2002) Intervention with environmental enrichment after experimental brain trauma enhances cognitive recovery in male but not female rats. Neurosci Lett 334(3):165–168.

Zhao YY, Li JT, Wang XD, Li YH, Huang RH, Su YA, Si TM (2013) Neonatal MK-801 treatment differentially alters the effect of adolescent or adult MK-801 challenge on locomotion and PPI in male and female rats. J Psychopharmacol 27(9):845–853. 0.1177/0269881113497613.

(Accepted 21 April 2015)
(Available online 29 April 2015)